Comparison of Depression Identification after Acute Coronary Syndrome: Quality of Life and Cost Outcomes

Manual of Operations

Version 5

Last updated 1/1/2019

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Administrative Information

Title Registration Data

Scientific Title: Depression Screening RCT in ACS patients: Quality of Life and Cost Outcomes (Acronym: CODIACS QoL)

Public Title: Comparison of Depression Identification after Acute Coronary Syndrome

Trial Registration: ClinicalTrials.gov: NCT01993017

Secondary Identifiers: Columbia University: IRB AAAK9253
Duke Clinical Research Institute
Health Partners Institute for Education and Research
Kaiser Permanente Northwest – Center for Health Research

Funding Agency: NHLBI
Application Number: 1 R01 HL114924-01A1

Primary Sponsor: Columbia University

Collaborators: Duke Clinical Research Institute
Health Partners Institute for Education and Research
Kaiser Permanente Northwest – Center for Health Research

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Countries of Recruitment: USA only

Health Condition(s) or problem(s) studied: Acute Coronary Syndrome
Depressive symptoms
Health care utilization

Interventions: Randomization to no depressive symptom screening (No Screen), depressive symptom screening with physician notification of elevated depressive symptoms (Screen & Notify), or depressive symptom screening and participant-selected treatment for those with elevated depressive symptom levels: pharmacologic (sertraline), behavioral (Cognitive Behavioral Therapy), a combination of both treatment modalities or neither (Screen, Notify & Treat).

Key Inclusion and Exclusion Criteria*:

Inclusion criteria:
English or Spanish[†]-speaking participants
Documented ACS within the past 2-12 months
Age 21 and older
Has access to phone or computer

Exclusion Criteria:
Unable to speak English
Less than 21 years of age
Terminal illness (life expectancy <1 year as determined by physician/medical record)
Psychiatric exclusions: dementia, history of bipolar disorder, psychosis, major depression,
suicide attempt or self-inflicted injuries, current alcohol or substance abuse, and/or currently
receiving depression treatment.

**fully defined in the 'Eligibility Criteria Section'*
[†]Spanish-speaking participants recruited from Columbia-site,only

Study Type: 3-arm parallel group Randomized Controlled Trial

Date of First Enrollment: February 6, 2014 (Kaiser site)
Target Sample Size: 1500 enrollees

Recruitment Status: Actively enrolling
Primary Outcomes: To examine the benefits and costs of the AHA's advisory for depression screen and treatment of post-ACS patients.

Key Secondary Outcomes: Cost/Health Care Utilization

MOP Version: 5

Funding: NHLBI R01 HL114924-01A1

Roles and Responsibilities

Project PI:
Dr. Ian M. Kronish, Associate Professor of Medicine, and the Associate Director of the Center for Behavioral Cardiovascular Health at Columbia University assumed the role of sole-PI in 2017. The project was initially led by Dr. Karina Davidson. Dr. Kronish had been the Columbia site-PI since 2015, became MPI with Dr. Davidson in 2016 prior to becoming sole-PI. Dr. Kronish's main role in this project will be to lead this interdisciplinary team in the operational conduct of this trial, including supervision and quality control for all staff, ensuring timelines are met, and problem-solving barriers to successful study management. He will also contribute to the dissemination of all results, and ensure that co investigators and collaborators have the opportunity to contribute to these dissemination efforts. Dr. Kronish's responsibilities include:

- Overseeing and coordinating all clinical components and training for the trial, including
  implementation, administration, supervision of research staff, communication and coordination with the three sites and all budgetary expenditures
- Chairing telephone meetings of the Steering Committee, which will plan and implement all study policies and procedures, including interfacing with the Data Safety and Monitoring Board
- Supervising the clinical coordinating Center personnel
- Coordinating the preparation of all reports, data sharing documents, meeting abstracts, presentations and manuscripts for publication, and the release of the final data set (in collaboration with Dr. Ken Cheung and Site Investigators).
- Serving as the liaison to the National Heart, Lung and Blood Institute.

Dr. Kronish is trained in internal medicine, is past director of a primary care-based mental health collaborative care depression program, and is experienced at leading RCTs relevant to behavioral medicine, and thus is well-qualified to direct this multi-site RCT.

Site PIs:

Karen Margolis, MD from **HealthPartners** has participated for many years in large, multi-center randomized trials studying cardiovascular disease, including landmark studies such as ALLHAT, ACCORD, and the Women's Health Initiative. She has intimate knowledge of the methods for recruitment and retention of a trial cohort, as well as how to maintain scrupulous attention to carrying out pharmacological and behavioral interventions according to a study protocol. Dr. Margolis has considerable experience with using electronic data to appropriately target and cost effectively recruit participants for a wide variety of clinical trials. In her role as site PI, Dr. Margolis will oversee all aspects of the successful implementation of the study.

Rowena Dolor, MD has been the Director of the Duke **Primary Care Research Network (PCRN)** since 1997, and has participated in over 70 trials and studies on hypertension, diabetes, depression, anticoagulation, hyperlipidemia, obesity, asthma, otitis media, and vaccines. She works closely with her sites to ensure that proposed trials (a) answer an important question aimed towards improving patient care and clinical outcomes (b) are designed to minimize the burden on practice staff to participate

in the research study and does not interfere with clinic workflow, and (c) results are disseminated back to the practices at the end of the project. PCRC was involved in ARTIST, an RCT to investigate the effectiveness and outcomes of primary care patients who were randomized to one of three SSRIs, and her system enrolled 248 patients in a 6-month period (results published in JAMA). Dr. Dolor also has expertise in cardiovascular disease; she co-authored the AHA Preventive Cardiology guidelines in women published in 2007 and 2011. Dr. Dolor's role includes practice and patient recruitment, advising the investigative team on how to implement the study within a busy primary care environment, dissemination and implementation of the study findings, as well as collaborating on all aspects of study procedures.-

Gregory N. Clarke, PhD is a Senior Investigator and Assistant Program Director at Kaiser-Permanente's Center for Health Research (KP-CHR). Dr. Clarke has been conducting mental health research for 20 years and his areas of interest include depression treatment/prevention, child and adolescent mental health and treatments, and treatment of substance abuse comorbid with mental disorders. Dr. Clarke has been the principal investigator and co-investigator of several grants funded by the National Institute of Mental Health, conducting controlled outcomes trials of depression treatment and prevention in at-risk populations. Some of his most recent controlled trials examine the costs and clinical outcomes of preventing and treating depression in adolescent offspring of depressed parents enrolled in an HMO; the medication and psychotherapy treatment of depression in adolescents who have failed to respond to an initial course of SSRI anti-depressant medication; treatment of depression in adults also receiving outpatient treatment for alcohol addiction; simultaneous psychotherapy and medication for depressed adolescents treated in primary care; and Internet self-care programs for depressed adults and adolescents. In his role as site PI, Dr. Clarke will oversee all aspects of the successful implementation of the study at KP-CHR.

Nathalie Moise, MD, MS
Dr. Moise is an Assistant Professor of Medicine at Columbia University and a board-certified internist. Her program of research involves developing and testing strategies to increase the implementation of cardiovascular and behavioral guidelines relevant to primary care. She also conducts research to increase the understanding of the impact of psychosocial factors on cardiovascular disease outcomes. She has served as a co-I on multiple federally-funded trials testing behavioral interventions for cardiovascular disease. She also actively treats patients with acute coronary syndromes and depression on the inpatient and outpatient setting. Dr. Moise assumed the role of site-PI of the Columbia University site from Dr. Kronish in 2016.

Co-Investigators:

Karina Davidson, PhD
Dr. Davidson is Dean of Academic Affairs Senior Vice President of Research for Northwell Health. Dr. Davidson was the sole PI of this trial from 2013-2015, became MPI with Dr. Kronish in 2016, and has been a co-I since 2017. Her current role is to facilitate dissemination of the trial results to the scientific community and the public.

Peter A. Shapiro, MD
Dr. Shapiro is a Professor of Clinical Psychiatry at Columbia University College of Physicians and Surgeons, and Director of the Psychosomatic Medicine Fellowship Program and Associate Director of the Consultation-Liaison Psychiatry Service at New York Presbyterian Hospital-Columbia University Medical Center. The focus of Dr. Shapiro's academic work has been on the treatment of depression in coronary artery disease and heart failure patients. He was a co-investigator for the SADHART studies of sertraline treatment after acute coronary syndromes as well as the COPES and CODIACS intervention trials.
Dr. Shapiro's background in clinical evaluation and treatment of depression in heart disease patients, use of quality of life measures in heart disease clinical trials, and collaboration in randomized clinical trials of depression treatment in heart disease make him highly qualified to serve as study psychiatrist. As in the COPES and CODIACS trials, Dr. Shapiro's primary operational roles will be advising on treatment decisions in stepped care reviews of participants randomized to the Depression Screen and Intervention arm of the trial and serving as a consultant for the site medication prescribers.

Daichi Shimbo, MD, MS
Dr. Shimbo is an Associate Professor of Medicine at Columbia University and a board-certified cardiologist. Dr. Shimbo has been involved in all of the depression—ACS studies conducted at the Center for Behavioral Cardiovascular Health. He will bring his expertise on ACS diagnosis and electronic medical record coding to ensure that sensitive and specific algorithms are used at each site for ACS patient selection. He will also ensure that the eligibility criteria are appropriately implemented, as he has done for previous trials. He will oversee the conduct of random site audits on approximately on 5% of all randomized participants to verify the appropriate classification of qualifying ACS events and provide feedback where discrepancies are found. Importantly, he will take the lead as the Medical monitor who will review all AEs and UAPs, and provide consultation to site staff in the collection and timely reporting of these events as needed. He will create a twice yearly report on these events for the DSMB. Drs. Davidson and Shimbo will jointly ensure adherence to established federal and institutional patient safety and protection guidelines. Dr. Shimbo will also advise on analyses of the data and will ensure that cost and medical decision-making information relevant to cardiology is presented within the disseminated manuscripts.

Ken Cheung, PhD
Dr. Cheung is Interim Chair and Professor of Biostatistics, in the Mailman School of Public Health at Columbia University. He has extensive experience conducting data analyses relevant to RCTs in the area of cardiovascular disease. Dr. Cheung will receive reports from Faith Parsons, the CBCH Data Manager (see below), regarding the data operations. He will also lead the primary outcome analyses relevant to this trial.

Consultants:

Joseph Ladapo, MD, PhD
Dr. Ladapo is Associate Professor of Medicine in the David Geffen School of Medicine at UCLA. He has expertise in conducting cost-effective analyses using data from large health systems. He has previously collaborated with CBCH investigators on cost-

effectiveness analyses relevant to the COPES and CODIACS RCTs which evaluated enhanced depression treatment interventions in post-ACS patients.

Coordinating Center Personnel:

Vivian Medina, MA, LCSW
Vivian Medina is a full-time, licensed clinical social worker with the Center for Behavioral Cardiovascular Health at Columbia University and is the Cognitive Behavioral Therapy Treatment Specialist for the trial. She has provided cognitive behavioral therapy and problem solving therapy for a number of trials for the past eight years, and she has done so in-person, by webcasting, and by telephone. Ms. Medina received training in PST from Dr. Mark Hegel, Professor of Psychiatry, Community & Family Medicine, and The Dartmouth Institute at the Geisel School of Medicine at Dartmouth and has always met therapy fidelity standards in all past trials. She will conduct cognitive behavioral therapy sessions for all sites for this study. In addition to extensive experience in the delivery of telephone-delivered therapy to study participants with cardiovascular diseases, Ms. Medina is fully bilingual and has successfully conducted cognitive behavioral therapy with both English and Spanish-speaking subjects. She will also attend the bi-weekly participant progress/safety meetings, and will consult Dr. Shapiro when needed.

Joan Duer-Hefele, RN, MA, CCRC
Ms. Duer-Hefele is the Center for Behavioral Cardiovascular Health's Nurse Manager and will function as Project Manager for this trial. In addition to the oversight of study operations and personnel, participant recruitment, and retention, Ms. Duer-Hefele will manage all quality assurance activities in consultation with study investigators.
Ms. Duer-Hefele is both a credentialed nursing administrator and certified clinical research coordinator. She has extensive training in human subjects protections and privacy practices. She has more than 25 years personnel management experience, the last 15 of which directly relate to the implementation of clinical research projects, including regulatory oversight and quality monitoring activities. In this project, Ms. Duer-Hefele's role will be to assume responsibility for the development of metrics related to study implementation and the continuous assessment of achievement to ensure timely progress toward study objectives. She will assume responsibility for facilitating the training and management of all study personnel, compliance with regulatory mandates, data integrity, quality assurance activities, and ensuring participant safety. She will report directly to Dr. Davidson, the Principal Investigator

Faith Parsons, BS
Ms. Parsons has three years of experience as the Data Manager for the CODIACS-I RCT Study, thus she is well acquainted with the study protocol. She will coordinate with Ms. MacMillan and the KP-CHR team in the creation of the centralized, web-based tracking and data entry system. She will also be responsible, under the direction of Dr. Muntner, for the management of the overall project data, and will prepare data reports for regular study team and DSMB meetings. Further, she will monitor the overall integrity of the study data by generating missing data and other relevant reports, and if necessary, work closely with study site personnel to resolve missing or inconsistent data. In the later years of the project, she will be responsible for preparing the data dictionary and dataset for data analysis activities.

Tara St. Onge, BS, RN
Ms. St. Onge is a research assistant at the Center for Behavioral Cardiovascular Health. She will assist Ms. Duer-Hefele in project management activities such as organizing communications amongst sites and coordinating the bi-weekly treatment and operations meetings.

Site Personnel:

This section can be customized for each site's coordinators and medication treatment prescribers.

Committees:

Data Safety and Monitoring Board
The Data Safety Monitoring Board (DSMB) is composed of four members as well as an ex officio representative from NHLBI.

Walter T. Ambrosius, PhD (Chairperson)
Professor, Department of Biostatistics
Director, Design and Analysis Unit
Wake Forest University School of Medicine

Richard C. Veith, M.D.
Richard D. and Bernice E. Tutt Endowed Professor in the Neurosciences
Chair, Department of Psychiatry and Behavioral Sciences
University of Washington School of Medicine

Stephen Lepore, Ph.D
Professor, Department of Health
Director, Social and Behavioral Health Interventions Laboratory
Temple University

Joseph A. Diamond, M.D
Cardiologist
Director, Nuclear Cardiology at Long Island Jewish Medical Center
North Shore, Long Island Jewish Medical Center

Catherine Stoney, Ph.D.
NHLBI Project Officer (Ex Officio)

Ms. St. Onge also serves as an executive secretary to the DSMB. The composition of the board includes individuals with expertise important to the present study and their appointments were made in consultation with NHLBI staff. The CODIACS-QOL DSMB follows NHLBI rules of formation and operation. All data concerning adverse outcomes will be reviewed by the Data Safety Monitoring Board on the schedule set by the DSMB. Serious events will be evaluated during a conference call any serious adverse effects will be reported to the IRB.

Steering Committee
The Steering Committee is the decision-making body for this study. It consists of the Principal Investigators for the study. The Steering Committee will develop policies and procedures under the direction of the Data Safety and Monitoring Board. The Steering Committee will direct the efforts of the Columbia coordinating center and the recruitment and successful retention of participants at each of the four sites HealthPartners Research foundation (Margolis, site PI), Duke University Primary care-based Research Network (Dolor, site PI), Kaiser Northwest (Clarke, site PI), and Columbia University Irving Medical Center (Moise, site PI). The NHLBI R01 funding is to CUIMC, and subcontracts will be established with each of the three sites. There will be no subject recruitment at CUIMC.

Operations Committee
The Operations Committee will help in addressing any operational issues that arise from each site during the duration of the study. This committee will be comprised of Joan Duer-Hefele, Faith Parsons, Tara St. Onge, and each of the sites' project managers and coordinators. They will meet bi-weekly with each site via telephone to discuss any protocol, operational, or data base issues. If major issues arise they will be brought to the attention of the PIs.

Treatment Committee
The Treatment Committee will be in charge of handling any treatment related issues from each of the three sites. The Treatment Committee will be comprised of Dr. Peter Shapiro and Vivian Medina LCSW, and the medication treatment specialist at each site. This committee will meet bi-weekly via phone to discuss any active cases.

Publications and Disseminations Committee
The Steering Committee will create a Publications and Dissemination Committee, led by PI Dr. Kronish, to facilitate the creation, publication, and dissemination of potential manuscripts that use study data.

Introduction

Background and Rationale

Patients with an acute coronary syndrome (ACS) and comorbid depression have a 2-fold higher risk for recurrent ACS and mortality, worse quality of life, and higher costs of care than non-depressed ACS patients. The strength of these observational findings prompted the American Heart Association (AHA) to advise that routine depression screening for ACS patients and referral for depression diagnosis and treatment as indicated occur. Unfortunately, there are no randomized controlled trials (RCT) to inform this large, potentially expensive screening recommendation. And, screening guidelines/advisories in the absence of RCT evidence have recently been extensively criticized (and withdrawn). This poses a serious dilemma for clinicians, health care systems, and for health care policy leaders. An RCT is urgently needed to provide evidence for these different constituents about the costs and benefits of the AHA depression screen and treat algorithm. Two critical gaps in knowledge must be filled to determine if public health would be improved by the AHA strategy for depression screening in post-ACS patients: 1) Does this strategy improve quality-adjusted life years for patients with a recent ACS (primary outcome)? and 2) Is the cost of providing depression screening and any type of depression treatment within the acceptable and typical amounts reimbursed for health care services?

Our **specific aim** is to determine the quality-adjusted life year benefits (primary outcome) and health care costs of following the AHA's advisory for depression screening and then referral for further diagnosis and treatment in post-ACS patients, if elevated depressive symptoms are found. To accomplish this aim, we will randomize patients from four different, geographically diverse health systems to three different groups: 1) to the AHA depression screen, notify, and treat if elevated depressive symptoms are found algorithm (intervention group) or: 2) to receive no depression screening (strong control group) or: 3) to be screened and a primary care provider notified of elevated depressive symptoms (minimally enhanced control group). Health-related quality of life, depressive symptoms, and costs will be obtained from all patients, so that the benefits and the costs of these three different depression screening strategies can be compared.

Depression and acute coronary syndromes (ACS) carry large world-wide public health burden, and their comorbidity is common. Multitudes of observational studies have convinced leading authorities to advise that ACS patients should be screened for depression, and then treated if it is detected. No randomized controlled trial exists to directly test if this strategy improves any outcome. This research is **significant** because it will provide vital randomized controlled trial (RCT) data from four different health care systems on cost-effectiveness and quality of life to inform national screening guidelines about the usefulness of depression screening and treatment in ACS patients

Objectives/Hypothesis

The overarching goal of this research is to conduct a state-of-the-art RCT that will rigorously evaluate the benefits and costs of AHA's depression advisory for modern post-ACS patients.

To examine in a randomized controlled trial the benefits and costs of the AHA's advisory for depression screen and treatment of post-ACS patients.

Hypothesis 1: Screen, notify, & treat intervention group will gain significantly more quality-adjusted life years (primary outcome) across 18 months when compared to No Depression screen control group, and also when compared to the Depression screen & notify control group.

Hypothesis 2: Those randomized to AHA's Depression screen & treat intervention group will have a favorable incremental cost-effectiveness ratio when compared to No Depression screen control and also when compared to the Depression screen & notify control group.

Trial Design

To accomplish these aims, we will randomize patients from four different, geographically diverse health systems to three different groups: 1) to the AHA depressive symptom screen and treat if elevated depressive symptoms are found (Screen, Notify & Treat intervention group) or: 2) to receive no depressive symptom screen (No Screen strong control group) or: 3) to be screened and a primary care provider notified of elevated depressive symptoms (Screen & Notify minimally enhanced control group). Health-related quality of life, depressive symptoms, and costs will be obtained from all participants, so that the benefits and the costs of these three different screening strategies can be compared.

Methods

Participant, Interventions and Outcomes

Study Setting: Coordinating Center

The Center for Behavioral Cardiovascular Health at Columbia University (CBCH) is a clinical research center in the Department of Medicine, Division of General Medicine at the Columbia University Irving Medical Center The Center currently has a staff and faculty of over 40 highly skilled interdisciplinary professionals (internists, cardiologists, psychologists, and quantitative faculty) engaged in more than 20 different interdisciplinary research studies investigating the behavioral and biological factors that explain the relationship between depression and heart disease, ways to treat depression in those with established heart disease, the psychosocial factors and biological mechanisms that contribute to hypertension, and alternative approaches to diagnosing and treating hypertension. CBCH serves as the Coordinating Center for this trial.

Study Setting: Recruitment Sites

Kaiser Permanente (KP-CHR), founded in 1946, was the country's first HMO. Currently, national Kaiser membership exceeds 9,000,000. **KP-CHR** is a professional autonomous multi-disciplinary research organization housed within one of eight semi-autonomous regions of the country's first and largest not-for-profit HMO and services approximately 475,000 members in northwest Oregon and southwest Washington. Clinical outpatient facilities include approximately 30 comprehensive ambulatory clinics located across this metro area. A large proportion of the hundreds of RCTs that have been conducted at CHR during its 48 years in operation are those focused on depression, cardiovascular diseases and other chronic conditions, many of which included cost effectiveness analyses.

HealthPartners is the largest consumer-governed nonprofit health care organization in the country, providing care, coverage, research, and education to improve health and well-being in partnership with its members, patients and community. Included under HealthPartners' umbrella are Regions Hospital (a tertiary-care hospital in St. Paul, MN), Park Nicollet HealthPartners Care Group, HealthPartners Center for Memory & Aging, Park Nicollet Methodist Hospital (a 426-bed facility with more than 960 physicians in St. Louis Park, MN) and HealthPartners Institute for Education and Research. HealthPartners has formal relationships with hospitals and clinics throughout Minnesota and western Wisconsin, including Westfields Hospital (New Richmond, WI), Lakeview Hospital (Stillwater, MN), Hudson Hospitals and Clinics (Hudson, WI) and Physicians Neck and Back Clinic (Roseville, MN).

Founded in 1957, the HealthPartners family of care serves more than 1.5 million medical and dental health plan members and more than1 million patients. In 2013, HealthPartners and Park Nicollet Health Services combined under the name HealthPartners and a single consumer-governed board of directors. The new organization includes a multispecialty group practice of more than 1,700 physicians; seven hospitals; 47 primary care clinics; 22 urgent care locations; 22 dental clinics; and numerous specialty practices in Minnesota and western Wisconsin. HealthPartners is

the top-ranked commercial health plan in Minnesota and is also ranked among the top 30 plans in the nation, according to the National Committee for Quality Assurance's Health Insurance Plan Rankings 2012-2013. For more information, visit www.healthpartners.com.

Park Nicollet HealthPartners Care Group has physicians practicing in more than 35 medical and surgical specialties. Access to data from the primary care clinics, hospitals and the International Health Center and specialty centers allows HealthPartners Institute for Education and Research to conduct research on large patient populations and subpopulations.

Regions Hospital, the site of the Institute's IRB and other committees, serves a culturally, economically and ethnically diverse population. The hospital is the state's second largest provider of charity care. Regions features the Center for Undergraduate and Graduate Clinical Education, a full medical library, a psychiatric unit associated with the emergency department, an HIV/AIDS program, digestive care center, birth center and same-day surgery. The 54,000-square-foot emergency department has 53 beds and an 11-bed mental health crisis unit and onsite radiology and lab services.

The Duke Clinical Research Institute (DCRI), a multidisciplinary group of faculty and staff from the Departments of Medicine, Surgery, Anesthesiology, Pediatrics, Community and Family Medicine, and the Heart Center at Duke University Medical Center is fully committed to this project and will supplement as needed the resources that are described in the proposal. The Duke Primary Care Research Consortium (PCRC) is a primary care research network composed of academic and community practices within the Duke University Health System (DUHS) and surrounding communities. The PCRC is organizationally placed within the Duke Clinical Research Institute (DCRI). For the proposed study, we will work with 15 primary care practices that are part of the network. The PCRC has participated in over 70 studies on hypertension, diabetes, depression, anticoagulation, hyperlipidemia, obesity, asthma, otitis media, and vaccines, and is often the lead recruiting sites on these national trials.

Columbia University Irving Medical Center-New York Presbyterian is comprised of an academic medical center (CUIMC) that forms the largest campus of the New York Presbyterian (NYP) health system. The four major divisions of NYP are the aforementioned hospital, the NYP Regional Hospital Network, NYP Physician Services, and NYP Community and Population Health. With more than 1,800 physicians, surgeons, dentists, and nurses in locations throughout the New York City metro area, CUIMC-NYP provides comprehensive patient care and offers a range of general and specialized medical, dental, and nursing services.

Detailed Eligibility Criteria

Inclusion Criteria

Criteria	EMR Verification and ICD-9 Codes
English or Spanish*-speaking participants *Spanish-speaking participants eligible at Columbia-site, only	Primary language designation in EMR (if available) Participant attestation
Documented ACS within the past 2-12 months	Evidence of one or more of the following within the past 2-12 months: (1) Diagnosis of acute myocardial infarction (410) during an inpatient hospitalization (2) Diagnosis of unstable angina (411) during an inpatient hospitalization with a history of coronary artery disease (414) 410.00-410.92 Acute Myocardial Infarction 411.00-411.89 Other acute and sub-acute forms of ischemic heart disease 414.00-414.9 Other forms ischemic heart disease
Over the age of 21 years	DOB
Has access to a phone and/or computer	Participant confirmation of phone number listed in EMR

ICD 9 discharge codes of 410 (acute myocardial infarction) through EMR searches have excellent positive predictive value when clinical data are abstracted and checked by two coders blinded to discharge code. Thus, we will use this discharge code for ACS eligibility. We will furthermore select potential participants with ICD 9 code hospital discharge codes of 411 (unstable angina), who also have established coronary artery disease (ICD 9 code of 414) to ensure that participants meet the definition of an ACS, as described in ACS case definitions by numerous cardiology societies. This approach – having broad eligibility – provides for a high degree of generalizability.

Medical Exclusion Criteria

Terminal illness defined as, but not limited to:
NYHA class IV, ACC class D CHF requiring inotropes or mechanical assist devices or critical aortic stenosis without plan for correction
End-stage COPD/emphysema
Advanced cirrhosis with encephalopathy, varices, severe ascites

Severe rheumatologic diseases requiring frequent hospitalizations, and multiple cytotoxic agents and/or disease modifying drugs
Metastatic pancreatic, esophageal, colorectal or stomach cancer
Metastatic sarcoma, ovarian, melanoma or renal cell cancer
Metastatic breast cancer with multiple recurrences despite treatment
Advanced CNS malignancies
Recurrent hematologic malignancies with multiple recurrences despite treatment
Persistent AIDS, untreated or treated
Currently pregnant

Participant Reported Screening Exclusions

Potential participants will complete a brief screening questionnaire to confirm that they have none of the above conditions, that they speak English and that they are interested in being enrolled in the study

Interventions

The 1500 participants who meet eligibility and indicate a willingness to participate and potentially receive treatment will then be randomized. Those randomized to the AHA Depression Screen, Notify & Treat or Depression Screen & Notify groups will then complete assessment of depressive symptom severity, while those randomized to No Depression Screen group will not. All participants will be followed according to the same schedule of assessments.

Overview of Visit Schedule & Measures. The overall guiding rationale for all visit and measure choices was to be cost-effective, brief, and convenient to the participant. The three participating health care organizations have different methods of recruiting however; they will all utilize an electronic medical record (EMR) algorithm to identify medically eligible patients. At the **EMR eligibility** stage, electronic medical records will be screened for documented ACS, age, language preference, and all other medical and psychiatric eligibility criteria. Patients identified as potentially eligible through this process may be contacted by mail, postcard, or email and offered either an email address or telephone number to contact if interested in study participation. This initial contact may include a study brochure, letter on behalf of their primary care provider, and/or a copy of the Informed Consent Form. Patients who express interest can either be screened and introduced to the consenting process over the phone, or scheduled for an in-person study screening and consent visit depending upon local practices and IRB approval.

In general, those who do respond by email or phone within approximately 2 weeks after the date of initial contact will be telephoned by the recruitment staff. We will carefully document who did not complete screening, who was ineligible (and for what reason) and who refused. Patients who consented and are eligible after screening will then be randomized during either the initial telephone call, a follow-up phone call or at an in-person visit. Participants who are randomized to Depression Screen & Notify arm will complete a PHQ-8 assessment, and those with clinically significant scores (≥ 10) will have a letter or electronic message sent to their PCP and/or cardiologist. Participants

who are randomized to the AHA Depression Screen, Notify & Treat arm will also complete a PHQ-8 assessment, and those with clinically significant scores (≥ 10) will be offered the option of receiving treatment for their depressive symptoms. Participants will be presented with the option of receiving medication therapy (sertraline or bupropion), Cognitive Behavioral Therapy (delivered via phone), a combination of both therapies or neither therapy. Depending on their treatment choice, they will be scheduled for their initial treatment visit, ideally within two weeks of randomization. Their PCP and/or cardiologists will also be notified if they have clinically significant scores (≥ 10) on the PHQ-8 assessment. Those randomized to No Depression Screen group will not receive the depression screen PHQ-8 at baseline.

All participants, regardless of randomization assignment, will complete the CES-D10, SF-12 health-related quality of life measure, symptoms checklist and lost productivity at enrollment and after 6-, 12-, and 18-months of study participation. All participants will also complete the PHQ-8 assessment at 18-months, with referral to treatment for those with scores ≥ 10. Participants will be contacted by telephone, or have an in-person visit scheduled, as they prefer. These administration methods have been compared in past studies and found to be equivalent. These follow-up contacts will be brief, and scheduled at the participant's convenience wherever possible.

All participants will report their health service utilization at 6-, 12- and 18-months. Additionally, all will have EMR searches of health care utilization extracted for the 18-month duration of the trial.

Outcomes

Quality-adjusted Life Year Assessment (Primary). Following the precedent set by RCTs with other depressed medical populations, we chose **the Short Form Health Survey (SF-12)** questionnaire to assess health related quality of life for the economic analysis. The SF-12 uses Likert scales to assess health-related quality of life aspects that are most directly relevant to depressed post-ACS patients: mobility and physical activities, ability to self-care, ability to perform usual activities, pain, and anxiety/ depression. Extensive validation, including construct validity, published normative data, and sensitivity to change have all been published for this scale. It has been used extensively the cost-effectiveness of a screening or intervention practice, and has successfully been used in depression interventions with other patients, allowing comparability with other data and settings. It is ideal for using in mail or web surveys, and takes less than 5 minutes. The NICE group in Britain recommends its use for providing cost and QALY data. We will collect deaths/dates of death from the national death index & EMR.

Depression Symptom Assessment. The AHA advisory suggests using the PHQ-2 (yes-no version) first, and then the full PHQ-8 for the assessment of depression symptom severity. In CODIACS QoL we will not utilize the PHQ-2, and instead ask all 8 items of the PHQ-8. The PHQ-8 has excellent psychometric properties, including sensitivity to successful change from treatment, good test-retest reliability when no treatment is offered, construct validity, reasonable correlations with health-related quality of life measures, and the ability to approximate likelihood of a major depressive

disorder. Scores on the PHQ-8 range from 0- 24 and a score of ≥10 is used for detecting likely depressive disorder, and clinically significant depression levels.

CES-D10. The Center for Epidemiologic Studies Depression Scale (CESD) is a screening measure (NOT a diagnostic tool) developed to identify current depressive symptomatology related to major or clinical depression in adults and adolescents. The CES-D10 is a short version of the original 20-item scale. The scores range from 0 to 30, and a score of 10 or greater is considered significant.

Depression-free Days. These will be calculated by using linear interpolation to estimate daily depression severity from the CES-D10 obtained at each of the four assessment points for all groups.

Health Service Utilization. A participant self-report tool used in documenting visits to health care providers, medications taken for anxiety and depression, emergency room visits and hospitalizations.

Loss of Productivity. A participant self-report tool used to document the nature of employment and absences due to health problems.

Overview of Cost/Health Care Utilization Data.

Costs to be collected for the trial	From electric medical record	From patient report
Antidepressant cost, therapy cost, other mental health visits	X	X
Depression-free days		X
Primary care visits, ED/urgent care, other medical visits, diagnostic services, inpatient services other outpatient services	X	
Days able to work/impact on work and leisure productivity		X

We will generate cost data using a combination of EMR extraction and patient surveys as detailed in the table above. We will calculate the cost of all possible depression care used (antidepressant cost and therapy cost. We will also collect data on all non-study delivery of depression treatment utilization from patient report and EMR. To derive other healthcare costs, we will use the EMR to collect data on all episodes of non-depression related healthcare utilization during the 18-month trial period: outpatient visits, ED/urgent care, as well as all in-patient care and any diagnostic tests or services. Average Medicare reimbursement rates according to diagnosis-related groups will be applied to inpatient visits to estimate hospitalization costs, and the Medicare fee schedule will be applied to outpatient and ED resource use according to current

procedural terminology codes. Finally, to calculate costs and potential cost-offsets from a societal perspective, we will collect participant report data on time lost from work. Lost productivity is believed by many experts to be assessed in our measure of health-related QoL instrument, the SF12. However, a sensitivity analysis will be conducted to test this assumption.

Participant Timeline

Table 1. Schedule of screening, baseline and follow-up forms

Form Name	Screening	Baseline	6 Months	12 Months	18 Months
Screening Questionnaire	X				
Subject Contact Information		X			
Subject Contact Information Update Form (if indicated)			X	X	X
Demographics		X			
PHQ-8		X*			X
CES-D10		X	X	X	X
SF-12		X	X	X	X
Health Service Use Questionnaire			X	X	X
Symptoms Checklist		X	X	X	X
Lost Productivity Questionnaire		X	X	X	X
Unanticipated Event Report			^	^	^
Quality Assurance Form**			X	X	X

*Participants randomized to the No Depression Screen arm will NOT complete PHQ-8 at baseline
** For blinded coordinator only
^Only completed if necessary

Sample Size

For the primary outcome in Aim 1, we will be making two primary comparisons: Difference in QALYs comparing AHA's Screen, Notify & Treat group vs. Screen & Notify and then separately to No Screen group. For choosing a sample size, we assumed a standard deviation for QALYs in the conservative control group (e.g., no depression screen) of 0.17. Additionally, based on a prior study of management of depression for patients with cancer, we assumed a net improvement in QALYs of 0.155 over 18 months of follow-up for individuals receiving the AHA's screen & treat intervention would be reasonable to expect. We assumed a 0.055 gain in QALYs for all participants not receiving treatment (i.e., those in the No Screen group, the Screen & Notify group and those without depression in the AHA's Screen, Notify & Treat group). An important consideration for this trial is that only 20% of patients randomized to the AHA's Screen, Notify & Treat group will meet criteria for depression and thus will receive the treatment part of intervention. Therefore, assuming an improvement in QALYs of 0.21 (0.055 background improvement + net improvement of 0.155) over the 18-month follow-up period for the 20% of participants with diagnosed depression and a 0.055 improvement in QALYs for the 80% of participants in this randomization group without depression, an overall gain in QALYs of 0.086 over the 18-month follow-up period can be anticipated in

this randomization group (0.21 * 0.2 + 0.055 *0.8 = 0.086). Thus, we anticipate a relative difference in QALYs of 0.031 (0.086 change in the AHA's screen & treat group minus 0.055 in the no screen group). We will have 80% statistical power to detect this difference of 0.031 with a sample size of n=475 participants in each group. We chose to determine sample size based on a pairwise comparison at 80% power in the two-step procedure, as a conservative approach relative to powering based on the F-test (See Statistical Analysis section, below, for further details). Specifically, under the scenario where one group has higher QALY than the other two by an effect size 0.18, the F-test will yield 84% power. Adding in 5% loss to follow-up, we selected an overall sample size of n=500 in each randomization group for an overall sample size of n=1500. Power analyses are typically based on the primary clinical outcome. We selected the QALY as our primary outcome and did not have specific economic hypotheses that required statistically tests. Therefore, we chose to follow this tradition, and do not present power calculations for our incremental cost-effectiveness ratios.

Recruitment

The four participating health care organizations have different methods of recruiting however, they will all utilize an electronic medical record (EMR) algorithm to identify medically eligible patients. At the EMR eligibility stage, electronic medical records will be screened for documented ACS, age, language preference, and all other medical and psychiatric eligibility criteria. Patients identified as potentially eligible through this process may be contacted by mail, postcard, or email and offered either an email address or telephone number to contact if interested in study participation. This initial contact may include a study brochure, letter on behalf of their primary care provider, and/or a copy of the Informed Consent Form. Patients who express interest may either be screened and introduced to the consenting process over the phone, or scheduled for an in-person study screening and consent visit depending upon local practices and IRB approval.

In general, those who do respond by email or phone within approximately 2 weeks after the date of initial contact will be telephoned by the recruitment staff. We will carefully document who did not complete screening, who was ineligible (and for what reason) and who refused. Patients who consented and are eligible after screening will then be randomized during the either the initial telephone call, a follow-up phone call or at an in-person visit. Participants who are randomized to Depression Screen & Notify arm will complete a PHQ-8 assessment, and those with clinically significant scores (≥ 10) will have a letter sent to their PCP and/or cardiologist. Participants who are randomized to the AHA Depression Screen, Notify & Treat arm will also complete a PHQ-8 assessment, and those with clinically significant scores (≥ 10) will be offered the option of receiving treatment for their depressive symptoms. Participants will be presented with the option of receiving medication therapy (sertraline), Cognitive Behavioral Therapy (delivered via phone), a combination of both therapies or neither therapy. Depending on their treatment choice, they will be scheduled for their initial treatment visit, ideally within two weeks of randomization, depending on their treatment choice. Those with clinically significant scores (≥ 10) in the Depression Screen, Notify, & Treat group will also have a letter sent to their PCP and/or cardiologist in the same manner as patients in the Screen & Notify group. Those randomized to the No Depression Screen group will not receive the depression screen (PHQ-8) at baseline.

Assignment of Interventions

Sequence generation

Participants will be randomly assigned to one of three groups: No Depression Screen, Depression Screen and Notify, or AHA Depression Screen, Notify and Treat. The randomization algorithm will be embedded in the web-based tracking system, using randomly assigned block sizes of 3, 6 and 9.

Concealment Mechanism

Participants will be randomized using the web-based tracking system. "User-roles" are assigned to study personnel, and the randomization tool is only available to unblinded coordinators at each site. Concealment will be ensured as the randomization algorithm will run in the backend, and only the randomization assignment will be visible to the unblinded coordinator after all necessary information about the participant has been entered.

Implementation

All eligible participants who give consent will be randomized by the unblinded coordinator after completion of all baseline assessments. The randomization tool is only available to designated unblinded coordinators (UC) at each site. The UC will enter the required information in the tracking system, after which the participant's group assignment will be immediately available.

If the participant is randomized to the No Depression Screen arm, the UC will inform the participant that no further assessments are required.

If the participant is randomized to the Depression Screen and Notify arm, the UC will administer the PHQ-8. If the PHQ score is ≥ 10, the UC will notify the participant's primary care provider and/or cardiologist either through the tracking system, by email, or mail in accordance with their IRB requirements.

If the participant is randomized to the AHA Depression Screen, Notify, and Treat arm, the UC will administer the PHQ-8. IF the PHQ score is ≥ 10, the UC will inform the patient of the available treatment options. Depending on the participant's choice of treatment, the UC will facilitate the initial contact with the relevant treatment specialist(s), ideally within two weeks of randomization and will work closely with the treatment specialist(s) to monitor the participant's treatment progress. The participant's PCP and/or cardiologist will also be notified of the positive depression screen.

Blinding

The blinded coordinator (BC) will administer all study regular assessments at 6-, 12- and 18-months, and will not be allowed to know the participants' group allocation, and this is ensured by the "user-role" designation in the tracking system. In addition to the UC, and due to the nature of the study treatment, participants, site PIs, and other personnel not designated as BC, cannot be blinded to the group allocation, but are encouraged not to disclose the allocation either at or when assisting the BC in scheduling follow up assessments. After each study visit, the BC will complete a 1-item questionnaire asking if the participant disclosed if they were in treatment. This information will be tracked, however no intervention will occur if the BC becomes unblinded.

Data Collection, Management and Analysis

Data Collection Methods

Screening

Screening will be accomplished in two stages. First, an EMR search of ICD-9 codes matched against the study eligibility and exclusion criteria will be used to identify eligible participants. The following ICD-9 discharge codes will be used to match eligibility criteria, 410 (acute myocardial infarction), 411 (unstable angina), 413.9 (angina pectoris NEC/NOS), 414 (coronary artery disease). Codes were updated for ICD-10 in later years of recruitment. Then, those who express interest will complete a short Screening Questionnaire to verify that none of the exclusion criteria apply to them.

Baseline and Follow-Up Assessments

Research data for the study include:

- Participants' responses to self-report assessments and measures including, demographics, CES-D10, quality of life (SF-12), symptoms checklist, health service use, and lost productivity, and unanticipated events
- Electronic medical record (EMR) data extraction

There will be four study visits/interviews: baseline, and three follow-up visits/interviews, at 6-, 12, and 18-months after enrollment. The list of forms and the schedule of collection is found in **Table 1** above. Personally identifiable information (PII) and protected health information (PHI) will be collected, and will be used to contact participants for follow-up visits, treatment delivery (if applicable), and to conduct a National Death Index search within 5 years after the study ends. Only authorized personnel, who have official status as part of the authorized research team, will have access to any records containing PII and PHI.

Treatment-Related Information

Study forms/guidelines are available to study treatment specialists to aid them in monitoring depressive symptoms, and tracking the progress of participants undergoing treatment. These forms are provided for the treatment specialists' convenience, and not for data analysis, and are included in the intervention manual.

Healthcare Utilization Data

Healthcare utilization data from date of enrollment to 18-months after will be downloaded from the integrated medical record systems at each site and delivered to Columbia University via secure electronic file transfer.

Data Management

Data Entry, Security and Storage

A dedicated, HIPAA-compliant, web-based tracking and data entry system created by KP-CHR will be used for this study. Baseline and follow-up self-report data will be collected in one of two ways: (1) the BC will complete the assessments with the participant over the phone or in-person, and will directly enter the responses on the web-based system, or (2) the blinded assessor completes the assessment using pen and paper forms, and either the BC or other research personnel will enter the data at a

later time. All data are stored in a secure server at Kaiser Permanente, and automatically backed up according to an established regular schedule.

Tracking Screened Subjects
Local study sites will manage the tracking of all participants approached for the study, and will document who completed screening, who was ineligible (including reasons for exclusion), and who refused. An aggregated report of the screening outcome will be sent to Columbia University for the biweekly operations meetings.

Tracking Enrolled Participants
Tracking of enrolled participants will be managed through the web-based tracking system using a 'to-do-list' mechanism. When a participant comes in window for a follow-up visit, his/her ID number will appear in the 'to-do list' section of the study personnel's page on the tracking system. All contacts and communication attempts with the participant, including study payments, will also be logged in the tracking system.

Data Discrepancies and Resolutions
Data discrepancies and missing data reports from baseline, follow-up visit, and treatment-related information will be generated either (1) automatically by the web-based tracking system, or (2) by running program code(s) created by the data manager. The data manager will send a list of errors and detailed descriptions to the project managers for resolution. All sites are required to address all items in the report by checking available documentations to correct any inconsistency, or by declaring the item as permanently missing. The local sites' study personnel will be responsible for updating and correcting the data entry in the web-based system within two weeks of receipt of the report.

The data manager, will work with the study statistician and health economist, to check all variables from the EMR data extraction for outliers, consistency and completeness. A detailed report will then be sent to the site project managers to resolve any data inconsistencies and discrepancies. Resolutions to data queries from EMR data will be expected at the soonest possible time.

Statistical Methods
All analyses will use the principle of intention-to-treat. Baseline characteristics will be examined as means (standard deviation) or percentages by randomization assignment to confirm a balanced allocation. As randomization will be performed stratified by study site, we will also assess baseline characteristics further stratified by study site. Also, participant characteristics will be compared across study site

Hypothesis 1:
Those randomized to AHA's Depression Screen, Notify & Treat intervention group will gain significantly more quality-adjusted life years across 18 months when compared to No Depression Screen control group, and also when compared to the Depression Screen & Notify control group.
We will compare outcomes for participants randomized to each of the three groups. Change in QALYs from baseline through 18 months post-randomization will serve as the primary outcome for this trial. First, quality of life utilities will be calculated using participants' scores on the SF-12 at each visit (baseline [pre-randomization] and 6, 12,

and 18 months post-randomization). All participants who complete the SF-12 will be classified according to the SF-6D. The SF-6D describes 18,000 health states. The average profile for each randomized group will be calculated. A multiple regression formula that applies weights will be used to assign quality of life utilities for each participant. Next, QALYs will be derived by multiplying the SF-6D derived quality of life utilities by 0.5 years for each 6 month-period, assuming linearity for changes in utility within each period. Any mortality events will be assigned zero QALYs from that point to the end of follow-up. With these scores calculated, we will calculate the average QALY gained (or lost) in each randomized group compared to assuming the utility calculated at baseline remained constant across 18-months.

The goal of the primary analysis is to identify whether there is difference in QALYs among the three groups. We plan to perform a two-step gate-keeping test procedure: We will first perform an F-test using ANOVA, and then proceed to do all three pairwise comparisons using two-sided t-test at 5% nominal significance *only if* the F-test has a p-value less than 0.05. With three randomization groups and three pairwise comparisons, this two-step procedure has been shown to preserve the familywise error rate in the strong sense, that is, a false positive comparison will occur at most with 5% probability under all possible scenarios.[46,47] This method is also generally more powerful than Bonferroni's adjustments.

In a secondary analysis, we will use a mixed model with a random intercept to assess the change in quality of life utilities over time comparing individuals in the AHA Screen, Notify & Treat group vs. the other two randomization groups. This model will incorporate main effects of time (i.e., baseline, and 6-, 12-, and 18-months post-randomization), treatment group, and the time by treatment group interaction. Using this model, we will be able to calculate the mean utility at each follow-up time period for the 3 groups and determine whether the response profile differs by time across groups.

Hypothesis 2:
Those randomized to AHA's Depression Screen, Notify & Treat intervention group will have a favorable incremental cost-effectiveness ratio when compared to No Depression Screen control group and also when compared to the Depression Screen & Notify control group.

For this hypothesis, we will judge the cost effectiveness of AHA Screen, Notify & Treat group compared to the Screen & Notify group, then we will compare the Screen & Notify group to the No Screen group on the basis of incremental cost-effectiveness ratios. The base case analysis will adopt a societal perspective with respect to costs and health benefits. Costs will include all healthcare costs and lost productivity cost related to use of website/staff time for depression screening, and the cost of all possible depression care used (antidepressant cost and therapy cost, including the cost for telephone/webcam use). Costs will be denominated in 2012 dollars and discounted at an annual rate of 3% as per the Panel on Cost-Effectiveness in Health and Medicine. For health benefits, we will convert SF-12 scores to QALYs, using the four (pre-randomization, 6, 12, & 18 month) measured values. Incremental cost-effectiveness analyses for comparison of treatment groups will be calculated sequentially using the ratio of the difference in average cost per participant divided by the difference in average QALY gained.

Sensitivity Analysis

We will perform sensitivity analyses by adopting a range of 'best and worst case' scenarios for resource costs (including actual costs from the three health care systems, or from estimates obtained using charge-to cost ratios), a range of initial depression prevalence, and depression treatment benefit (including considerations of recall bias for self-reported measures). We will also recalculate the incremental cost-effectiveness ratios separately by health care system, so that a range by site can be presented. Multivariate Monte Carlo simulation will be used to obtain 95% confidence intervals for estimates of cost and effectiveness, which will be used to produce a range of incremental cost-effectiveness ratios to determine the robustness of our results. In addition, we will repeat we will repeat our baseline analysis and sensitivity analysis after restricting cost accounting to the payer perspective only.

Data Monitoring

Our procedures will follow the NHLBI guidelines on DSMBs that was released October 2011 (http://www.nhlbi.nih.gov/funding/policies/dsmpolicy.htm). Specifically, in consultation with NHLBI, 4 DSMB members have been appointed. The Board includes a psychiatrist, cardiologist, psychologist and biostatistician with experience in prospective interventional trials and behavioral and/or psychosocial cardiology trials. The chair will have additional duties to review past minutes, conduct the meetings and review minutes prepared by the executive secretary. The DSMB developed an operational plan during the first six months of the study. The operational plan is similar to current plans the principal investigator has developed for ongoing trials funded by NHLBI and consistent with NHLBI's Policy on Human Subjects Research: Data and Safety Monitoring Plans dated October 2011. The plan includes conflict of interest disclosure statements for each member, frequency and location of meetings, policies and procedures and dissemination of meeting materials, notification of NHLBI staff, data to be reviewed and procedures for evaluating data and reporting findings. The specific study functions and outcomes that the DSMB will review at each meeting include: dropout rate, baseline PHQ-8 scores, CES-D10 scores, and number receiving AHA diagnosis and treatment portions of the intervention protocol. The primary safety measures will be adverse events reports and 18-month PHQ-8 scores. Other items reviewed by the DSMB at each meeting will include: (a) data quality, completeness, and timeliness; (b)recruitment performance of each site; (c) adequacy of compliance with goals for recruitment and retention, including women and minorities; (d) protocol adherence; and (e) presence of factors that could adversely affect participant safety, study outcome or compromise data confidentiality.

The Data Manager, under the direction of Dr. Cheung, will provide the DSMB with data reports on numbers of participants recruited into the trial, participant outcomes, and serious adverse reactions on a twice-yearly basis, or as determined by the DSMB. All investigators on this grant will be the decision-making body to implement policies and procedures and follow directives of the DSMB. The DSMB will determine if unanticipated events are related to the study, whether the study's informed consent form and process needs to be modified, whether the study's procedures need to be modified and whether the study should be discontinued due to serious adverse outcomes in either the control groups or in the intervention group. All data provided will be provided in a blinded fashion. The Steering Committee will serve as an additional oversight body to determine if the DSMB should be asked to meet sooner than anticipated based on the operational plan.

Harms

Since CODIACS-QOL is a screening trial, and not a treatment trial, the DSMB did not outline a list of reportable adverse events. However, given the nature of our population, and that some trial arms will be receiving therapy(ies), we have listed unanticipated AEs that must be reported to the DSMB according to the following guidelines.

The risk to participants will be minimal as the subjects will receive at least their usual medical care. We know of no study that has found that the type of intervention proposed

here has been associated adverse risk. Any adverse event (AE) or unanticipated problem will be identified, responded to, recorded by the site investigator, who will in turn ensure that the information is passed on (see Table below). If the AE or problem is unexpected, related to study involvement, and puts the participant at increased risk, it will be reported to the local IRB immediately, in accordance with local policies. These events will also be reported to Columbia University, which will collect and disseminate the information to the other sites and the DSMB. All other AEs and problems will be reported at the time of the biannual DSMB meetings. As this is a screening trial with a commonly used instrument, it is expected that no such events will occur.

Adverse Events and Unanticipated Problems Reporting Timelines (modified from NHLBI guidelines on reporting SAEs and Ups)

What Event is Reported	When is Event Reported	By Whom is Event Reported	To Whom is Event Reported
Fatal or life-threatening unexpected, suspected serious adverse reactions	Within 7 calendar days of initial receipt of information	Investigator	Local/internal IRBs/Institutional Officials Study coordinating center (who in turn report to DSMB)
Non-fatal, non-life-threatening unexpected, suspected serious adverse reactions	Within 15 calendar days of initial receipt of information	Investigator	Local/internal IRBs/Institutional Officials Study coordinating center (who in turn report to DSMB)
Unanticipated Problem that is not an SAE	Within 14 days of the investigator becoming aware of the problem	Investigator	Local/internal IRBs/Institutional Officials Study coordinating center (who in turn report to DSMB

Should a study-participation related, unexpected adverse event occur, the study cardiologist (Dr. Shimbo) and/or study psychiatrist (Dr. Shapiro) will review the circumstances of the event and report accordingly to the DSMB. Any serious adverse effects will be reported to the CUIMC IRB. If any adverse outcomes might influence the continued participation of the participants, active participants will be informed. All participants will be provided contact information instructed to contact either the study coordinator or local PI in the event the participant would like to discuss any study-related issue or adverse event that arises.

Procedures for Side Effects Due to Study Antidepressants:
Participants will have all possible side-effects carefully described and explained before any course of anti-depressants is initiated. Site medication providers have undergone thorough training on the detection and management of side-effects with Dr. Shapiro, who remains available for consultation with the site medication prescribers. Below is an overview of what was taught, and will be followed for the trial:

Strategies for Managing Antidepressant Side Effects
General Strategies:
1. Explore whether the side effects are 'physical' or 'psychological'?
2. Wait and support. Many side effects (i.e., GI depressive symptoms with SSRIs) will subside over 1-2 weeks of treatment.
3. Lower the dose (temporarily).
4. 'Treat' the side effects (see below).
5. Change to a different antidepressant.
6. Change to or add psychotherapy.

Antidepressant Drug Interactions:
All antidepressants are metabolized by the P450 isoenzyme system in the liver. Certain antidepressants inhibit specific subtypes of P450 enzymes and this may increase blood levels in participants who are taking other medications metabolized by the same isoenzyme systems. Care is advised in participants who are taking medications with a narrow therapeutic window such as digoxin, warfarin, anticonvulsants, or theophylline. It is advised to **observe clinically for side effects** from such medications and **to recheck serum blood levels** of such medications as the dose of the antidepressant is titrated upwards.

Procedures for Discontinuation Syndrome:
Abrupt discontinuation of short acting antidepressants can lead to an uncomfortable antidepressant withdrawal syndrome. All participants choosing anti-depressants will have this carefully explained, and will be monitored (by self-report) for continued adherence to their prescribed anti-depressant. Any participant reporting symptoms consistent with withdrawal syndrome will be reminded that their symptoms could be due to cessation of anti-depressant adherence, and will be urged to taper, rather than cease their medication use. Tapering will also be considered as appropriate when at stepped care decision points, an alternative medication is recommended

Any AE or unanticipated problem will be identified, responded to, recorded by the site investigator, who will in turn ensure that the information is passed on. If the AE or problem is unexpected, related to study involvement, and puts the participant at increased risk, it will be reported to the local IRB immediately, in accordance with local policies. These events will also be reported to Columbia University, which will collect and disseminate the information to the other sites and the DSMB. All other AEs and problems will be reported at the time of the biannual DSMB meetings.

Auditing
Routine audits of data completion and timeliness will be overseen by the study data manager.

Ethics and Dissemination

Research Ethics Approval

This protocol and the template informed consent forms have been approved by Columbia University's Institutional Review Board (IRB) with respect to scientific content and compliance with applicable research and human subjects regulations. The, participant education and recruitment materials, data collection forms, and Intervention manual have also been approved by the CUIMC IRB. Any subsequent modifications will also be reviewed and approved by the CUIMC IRB. Respective local site IRBs are required to approve protocol materials and a site-specific informed consent form. Each study site must submit verification of IRB approval to the Coordinating Center prior to the initiation of study activities.

Subsequent to initial review and approval, Columbia University's IRB, and the responsible local IRBs will review the protocol at least annually. The overall PI and site PIs will make safety and progress reports to the IRBs at least annually and within three months of completion of study visits. or completion at his/her site. These reports will include the total number of participants enrolled, reports to the DSMB, and any other requested reports.

Protocol Amendments

Any modifications to the protocol which may impact on the conduct of the study, potential benefit of the patient or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendment will be agreed upon by the overall PI, site PIs and co-investigators, and approved by the DSMB and responsible IRB prior to implementation and notified to the health authorities in accordance with local regulations.

Administrative changes of the protocol are minor corrections and/or clarifications that have no effect on the way the study is to be conducted. These administrative changes will be agreed upon by the overall PI and site PIs, and will be documented in a memorandum. The responsible IRBs may be notified of administrative changes at the discretion of the PIs.

Informed Consent

The protocol and informed consent procedures will be approved by the Institutional Review Boards at each participating institution. Consent forms will be worded in language that a person with a 6th grade education can understand and will be available in English. At the time of enrollment, the staff member will give a complete description of the study to the participant in clear, easy-to-understand language. After reading and understanding the consent and the procedures, those who choose to participate will sign and date the consent.

All staff involved in this study will have completed and passed GCP and HIPAA training, and will have been provided with materials and instruction in the proper and ethical

manner in which consent should be obtained. If a web-based or telephone consent is obtained, it will comply with all GCP and HIPAA regulations, and be IRB-approved.

Confidentiality
As part of the process involved in obtaining written informed consent, all participants will be reminded that their responses are confidential and that they may refuse to participate in the study or withdraw at any time without explanation, and further, that such an action will in no way affect their future interactions with their health care provider or the participating Medical Center.

To ensure confidentiality, all study-related information will be stored securely at the study sites. When paper records are obtained, those containing names or other personal identifiers, such as locator forms, medical records, and informed consent forms, will be stored separately from study records identified by participant ID number. Forms, lists, logbooks, appointment books, and any other listings that link participant ID numbers to other identifying information will be stored in a separate, locked file in an area with limited access. All databases will be secured with password-protected access systems. Datasets for analysis will be associated with an individual participant only by an assigned identification number.

All staff will have all relevant IRB and HIPAA training in the protection of human subject participants (Good Clinical Practice).

Declaration of Interests
All investigative staff has reported any conflicts of interest to their local IRB as part of the protocol approval process.

Access to data
Only authorized personnel, those who have official status as part of the authorized research team, will have access to any records containing identifiable participant data. Study personnel at local sites will only have access to their own site's data, and will be limited by their "user-roles" (i.e. HealthPartners study personnel will only have access to HealthPartners participants, blinded coordinators will not have access to group allocation, or treatment information).

The Clinical Coordinating Center will oversee the intra-study data sharing process.

Post-trial care
Participants found to have clinically significant depressive symptoms (PHQ 8 score ≥ 10) at the 18-month visit/interview, will have their PCP and/or cardiologist notified.

Dissemination policy
Study results will be posted at ClinicalTrials.Gov within one year of study completion. Sites will be encouraged to send each participant a "Thank You" letter upon their completion of study participation. Additionally it is suggested that, when data is analyzed, a brief lay person summary of the trial results be disseminated through patient communications at each respective site. A Publications and Disseminations Committee will be formed, and this committee will then create a policy/guideline for

authorship and review process of manuscripts and abstracts for publication or conference presentations.

Comparison of Depression Identification

after Acute Coronary Syndrome:

Quality of Life and Cost Outcomes

STATISTICAL ANALYSIS PROTOCOL

LAST UPDATED: 1/1/2019

Table of Contents

1. SYNOPSIS OF THE STUDY

The goal of this study is to determine the quality-adjusted life year benefits (primary outcome) and health care costs of following the AHA's advisory for depression screening and then referral for further diagnosis and treatment in post-ACS patients, if elevated depressive symptoms are found. To accomplish this aim, we will randomize patients from four different, geographically diverse health systems to three different groups: 1) to the AHA depression screen, notify, and treat if elevated depressive symptoms are found algorithm (Screen, Notify & Treat intervention group) or: 2) to receive no depression screening (No Screen; strong control group) or: 3) to be screened and a primary care provider notified of elevated depressive symptoms (Screen & Notify; minimally enhanced control group). Health-related quality of life, depressive symptoms, and costs will be obtained from all patients, so that the benefits and the costs of these three different depression screening strategies can be compared.

2. STUDY DESIGN AND OBJECTIVES

2.1 Study Design

Investigator initiated, multicenter, 3-group (1:1:1) randomized clinical trial.

2.2 Objectives

The overarching goal of this research is to conduct a state-of-the-art RCT that will rigorously evaluate the benefits and costs of AHA's depression advisory for modern post-ACS patients.

To examine in a randomized controlled trial the benefits and costs of the AHA's advisory for depression screen and treatment of post-ACS patients.

Hypothesis 1: Screen, notify, & treat intervention group will gain significantly more quality-adjusted life years (primary outcome) across 18 months when compared to No Depression screen control group, and also when compared to the Depression screen & notify control group.

Hypothesis 2: Those randomized to AHA's Depression screen & treat intervention group will have a favorable incremental cost-effectiveness ratio when compared to No Depression screen control and also when compared to the Depression screen & notify control group.

3. RANDOMIZATION AND BLINDING

Sequence generation
Participants will be randomly assigned to one of three groups: No Depression Screen, Depression Screen and Notify, or AHA Depression Screen, Notify and Treat. The randomization algorithm will be embedded in the web-based tracking system, using randomly assigned block sizes of 3, 6 and 9.

Concealment Mechanism
Participants will be randomized using the web-based tracking system. “User-roles” are assigned to study personnel, and the randomization tool is only available to unblinded coordinators at each site. Concealment will be ensured as the randomization algorithm will run in the backend, and only the randomization assignment will be visible to the unblinded coordinator after all necessary information about the participant has been entered.

Implementation
All eligible participants who give consent will be randomized by the unblinded coordinator after completion of all baseline assessments. The randomization tool is only available to designated unblinded coordinators (UC) at each site. The UC will enter the required information in the tracking system, after which the participant’s group assignment will be immediately available.

If the participant is randomized to the No Depression Screen arm, the UC will inform the participant that no further assessments are required.

If the participant is randomized to the Depression Screen and Notify arm, the UC will administer the PHQ-8. If the PHQ score is ≥ 10, the UC will notify the participant’s primary care provider and/or cardiologist either through the tracking system, by email, or mail in accordance with their IRB requirements.

If the participant is randomized to the AHA Depression Screen, Notify, and Treat arm, the UC will administer the PHQ-8. IF the PHQ score is ≥ 10, the UC will inform the patient of the available treatment options. Depending on the participant’s choice of treatment, the UC will facilitate the initial contact with the relevant treatment specialist(s), ideally within two weeks of randomization and will work closely with the treatment specialist(s) to monitor the participant’s treatment progress. The participant’s PCP and/or cardiologist will also be notified of the positive depression screen.

Blinding
The blinded coordinator (BC) will administer all study regular assessments at 6-, 12- and 18-months, and will not be allowed to know the participants’ group allocation, and this is ensured by the “user-role” designation in the tracking system. In addition to the UC, and due to the nature of the study treatment, participants, site PIs, and other personnel not designated as BC, cannot be blinded to the group allocation, but are encouraged not to disclose the allocation either at or when assisting the BC in scheduling follow up assessments. After each study visit, the BC will complete a 1-item questionnaire asking if the participant disclosed if they were in treatment. This information will be tracked, however no intervention will occur if the BC becomes unblinded.

4. DEFINITION OF TARGET POPULATION AND STUDY SAMPLES

4.1 Target Population

This study aimed to enroll survivors of acute coronary syndromes without a prior history of depression who had experienced an ACS within the past 2 to 12 months and would be eligible for depression screening.

Detailed eligibility criteria are provided below.

Inclusion Criteria

Criteria	EMR Verification and ICD-9 Codes

English or Spanish*-speaking participants *Spanish-speaking participants eligible at Columbia-site, only	Primary language designation in EMR (if available) Participant attestation
Documented ACS within the past 2-12 months	Evidence of one or more of the following within the past 2-12 months: (3) Diagnosis of acute myocardial infarction (410) during an inpatient hospitalization (4) Diagnosis of unstable angina (411) during an inpatient hospitalization with a history of coronary artery disease (414) 410.00-410.92 Acute Myocardial Infarction 411.00-411.89 Other acute and sub-acute forms of ischemic heart disease 414.00-414.9 Other forms ischemic heart disease
Over the age of 21 years	DOB
Has access to a phone and/or computer	Participant confirmation of phone number listed in EMR

ICD 9 discharge codes of 410 (acute myocardial infarction) through EMR searches have excellent positive predictive value when clinical data are abstracted and checked by two coders blinded to discharge code. Thus, we will use this discharge code for ACS eligibility. We will furthermore select potential participants with ICD 9 code hospital discharge codes of 411 (unstable angina), who also have established coronary artery disease (ICD 9 code of 414) to ensure that participants meet the definition of an ACS, as described in ACS case definitions by numerous cardiology societies. This approach – having broad eligibility – provides for a high degree of generalizability.

Medical Exclusion Criteria

Terminal illness defined as, but not limited to:
NYHA class IV, ACC class D CHF requiring inotropes or mechanical assist devices or critical aortic stenosis without plan for correction
End-stage COPD/emphysema
Advanced cirrhosis with encephalopathy, varices, severe ascites
Severe rheumatologic diseases requiring frequent hospitalizations, and multiple cytotoxic agents and/or disease modifying drugs
Metastatic pancreatic, esophageal, colorectal or stomach cancer
Metastatic sarcoma, ovarian, melanoma or renal cell cancer
Metastatic breast cancer with multiple recurrences despite treatment
Advanced CNS malignancies
Recurrent hematologic malignancies with multiple recurrences despite treatment

Persistent AIDS, untreated or treated
Currently pregnant

Participant Reported Screening Exclusions

Potential participants will complete a brief screening questionnaire to confirm that they have none of the above conditions, that they speak English and that they are interested in being enrolled in the study

4.2 Intent-to-Treat Sample

Analyses will be conducted on an intent-to-treat sample. No analyses will be conducted on a per-protocol or safety analysis sample.

4.3. Safety Analysis Sample

Safety analyses will be conducted using the same sample as the primary efficacy sample, and an intent-to-treat analysis plan will be used.

5. DESIGN CONSIDERATION

5.1 Primary Statistical Hypothesis

Those randomized to AHA's Depression Screen, Notify & Treat intervention group will gain significantly more quality-adjusted life years across 18 months when compared to No Depression Screen control group, and also when compared to the Depression Screen & Notify control group.

5.2 Interim and Final Primary Analysis

Given the nature of a screening trial, no *a priori* stopping rules were planned. Interim analyses were planned for purposes of monitoring the study for safety concerns, only.

5.3 Primary Efficacy Analysis

Change in QALYs from baseline through 18 months post-randomization will serve as the primary outcome for this trial. QALYs were chosen as the primary outcome to facilitate comparisons of the effect of depression screening with other preventive interventions as well as to facilitate cost-effectiveness analyses and policy decisions. As QALYs do not directly assess depression, this outcome measure also minimized possible patient reporting bias as a result of lack of participant blinding or masking to condition. The goal of the primary analysis is to identify whether there is difference in the change in QALYs among the three groups. QALYs describe the duration of illness per years of survival, adjusted for quality of life experienced during that survival. One year in perfect health is equivalent to 1 QALY. All patients will complete a standardized measure of quality of life using the Short Form-12 Health Survey, Version 2™ (SF-12) at baseline, and again at 6-months, 12-months, and 18-months.[1] QALYs will be estimated from the SF-12 using the Short Form 6 Duration (SF6D) which converts data from 7 items in the SF-12 assessing 6 domains (physical functioning, role limitations, social functioning, pain, mental health and vitality) to QALYs.[2] Study patients who die during the study period will be assigned a utility score of 0 for assessments after the date of death. QALYs over 18 months will

be calculated as the area-under-curve by interpolating linearly the scores at the four assessments (baseline, 6-month, 12-month, 18-month). There were no data obtained or available for these measures between assessments. Change in QALYs will then be obtained by subtracting the QALYs that would have occurred if there was no change in the baseline utility score from the actual QALYs that were measured across 18 months. The analysis will follow the principle of intention-to-treat and will be conducted on each imputed dataset with the point estimate deriving from the average of 5 datasets and the pooled variance calculated using Rubin's formula.

To determine the significance of differences, we will perform a two-step gate-keeping test procedure. This will involve first performing an F-test using ANOVA, and then proceeding to do all three pairwise comparisons using two-sided t-test at 5% nominal significance *only if* the F-test has a p-value less than 0.05. With three randomization groups and three pairwise comparisons, this two-step procedure can be shown to preserve the familywise error rate in the strong sense, that is, a false positive comparison will occur at most with 5% probability under all possible scenarios.[3,4] This method is also generally more powerful than Bonferroni's adjustments.

5.4 Sample Size Determination

The sample size of the trial was determined based on an assumed standard deviation for QALYs of 0.17.[5] Additionally, based on a general health-related quality of life outcome in a prior study of management of depression for patients with cancer, we assumed a net improvement in QALYs of 0.155 over 18 months of follow-up for depressed individuals who receive depression treatment in the Screen, Notify and Treat group.[6] We assumed a 0.055 gain in QALYs for all patients not directly linked to depression treatment (i.e., those in the No Screen group, the Screen & Notify group and those without elevated depressive symptoms in the Screen, Notify, and Treat group). An important consideration for this trial is that only 20% of patients randomized to the Screen, Notify and Treat group were expected to meet criteria for elevated depressive symptoms and thus, to receive depression treatment. Therefore, assuming an increase in QALYs of 0.21 (0.055 background improvement + net improvement of 0.155) over the 18-month follow-up period for the 20% of patients diagnosed and treated for depression in the Screen, Notify, and Treat group and a 0.055 improvement in QALYs for the 80% of patients in this randomization group without depression, an overall gain in QALYs of 0.086 over the 18 month follow-up period was anticipated in this randomization group (0.21 * 0.2 + 0.055 * 0.8 = 0.086). Thus, we anticipated a difference in QALYs of 0.031 (0.086 change in the Screen, Notify, and Treat group minus 0.055 in the No Screen group or Screen and Notify Group), leading to an expected effect size of 0.18 (= 0.031/0.17). With this effect size, we determined the sample size per group to be 475, which would yield 80% power for a two-sided t-test at 5% level. We chose to determine sample size based on a pairwise comparison at 80% power in the two-step procedure (described above), as a conservative approach relative to powering based on the F-test. Specifically, under the scenario where one group has higher QALY than the other two by an effect size 0.18, the F-test will yield 84% power. Adding in 5% loss to follow-up, we selected an overall sample size of n=500 in each randomization group for an overall sample size of n=1500.

5.5 Multiplicity

Our use of the 2-step gatekeeping function will enable us to preserve the familywise error rate in the strong sense, that is, a false positive comparison will occur at most with 5% probability under all possible scenarios.[3,4] This method will enable us to consider multiple group comparisons without using Bonferroni's adjustments.

5.6 Missing Data

CESD-10 questionnaire with missing data will be prorated if that participant answered more than 7 items. The missingness of data will then be assessed using Little's test. If data are found to missing at random, we will perform multivariated imputations to generate 5 imputed datasets by basing on covariates which were predictive of missing pattern such as input from prior visit and site variable; random sampling was used to impute the missing values at baseline. Missing data will be imputed sequentially, starting with the baseline visit, then the 6-month visit, followed by the 12-month and 18-month visits.

In sensitivity analyses, missing data will be handled by carrying the last observed value forward and by using best case-worst case scenario – in best case, we assumed that all missing had perfect health. In worst case scenario, we assumed all missing data had worst health status (QOL = 0).

6. BASELINE CHARACTERISTICS

Baseline characteristics will be examined as means (standard deviation) or percentages by randomization assignment to assess for a balanced allocation.

7. SAFETY/ TOLERABILITY

7.1 Primary (pre-specified) Safety Outcomes

Harms attributable to use of antidepressant medications (i.e., appetite problems, sleep problems, gastrointestinal upset, and bleeding) will be assessed through patient interview. Group differences in the prevalence of these potential adverse effects will be compared using chi-squared tests.

7.2 Mortality

Mortality will be assessed by surveying patient surrogates and through review of the electronic medical record. Group differences in mortality will be compared using chi-squared tests.

8. SECONDARY EFFICACY ANALYSES

Key secondary outcomes included depression-free days and health care costs.

Depression-Free Days

The prespecified secondary outcome will be cumulative depression-free days based on the 10-item Center for Epidemiologic Studies Depression (CESD-10) scale, a non-diagnostic,

epidemiologic, reliable and valid measurement for depressive symptoms, measured at baseline, 6-months, 12-months, and 18-months in all 3 arms.[7] *Depression-free days* will be calculated by using linear interpolation to estimate daily depression severity at each of the four assessment time points for the 3 study arms. Depression-free days is a valid and easily interpretable measure for estimating depression treatment outcomes when multiple measures of depressive symptoms occur over time. This measure is also amenable to cost-effectiveness analyses. In other trials, Depression-free days have been calculated using intervals as long as 6 months.[8] While a shorter interval (e.g., 3 months) can provide a more precise assessment of cumulative depressive symptoms over time, a 6-month interval was selected so as to avoid frequent communication between the study team and study participants. More frequent assessments could lead to increased behavioral support and could cloud the interpretation of the No Depression Screen group which was not intended to receive any behavioral interventions.

An epidemiologic instrument was chosen over a clinical measure of depressive symptoms as the use of a clinical measure would have mandated referral for depression treatment in those who screened positive in the No Screen group. The CESD-10 is a short version of the original 20-item scale. The scores range from 0 to 30. A score 4 or greater has been found to be the optimal cutpoint for a positive depression screen with a sensitivity and specificity of 97% and 84%, respectively, compared to a psychiatric interview in a sample of older adults.[9] Based on a review of the literature, we inferred that a cutpoint of 10 on the 10-item CESD would represent clinically significant depressive symptoms.[10]

The following rule will be used to convert CESD score to depression day

CESD < 4 -> 0 depression day

CESD = 4 -> 1/7 depression day

CESD = 5 -> 2/7 depression day

CESD = 6 -> 3/7 depression day

CESD = 7 -> 4/7 depression day

CESD = 8 -> 5/7 depression day

CESD = 9 -> 6/7 depression day

CESD >= 10 -> 1 depression day

Health Care Costs and Lost Productivity

The other prespecified secondary outcome will be Health Care Costs and Lost Productivity.[1] At baseline, 6-months, 12-months, and 18-months, patients will report measures of economic

[1]Cost of health care utilization was erroneously listed as a co-primary outcome on the initial clinicaltrials.gov entry. This error was corrected in clinicaltrials.gov on October 25, 2017, prior to completion of data collection or any interim data analyses. As can be seen in the planned statistical analyses, the sample size for the study was driven entirely by the change in QALYs outcome. Cost-effectiveness analyses, in contrast, were never intended to be listed as a co-primary outcome as they

productivity, including employment status, occupation, hours spent at work, and time lost from work for health-related reasons.[11] At 6-months, 12-months, and 18-months, patients will also report healthcare utilization since their last intake assessment, including emergency department (ED) visits, hospitalizations (location, admission and discharge dates), psychiatric medication use, name and dose, ambulatory care visits with mental health specialists, cardiologists, as well as PCPs and finally hospitalizations for cardiovascular events. Patient self-reports of healthcare utilization will be supplemented by review of the EMR and claims systems to collect data on healthcare utilization during the 18-month trial period. Average Medicare reimbursement rates according to diagnosis-related groups will be applied to inpatient visits to estimate hospitalization costs, and the Medicare physician fee schedule will be applied to outpatient and ED resource use according to current procedural terminology codes. Costs of study depression treatment will also be incorporated into estimates of healthcare utilization costs for those assigned to the Screen, Notify, and Treat group who agree to depression treatment by study personnel. To estimate economic costs from a societal perspective, changes in productivity and time spent traveling to appointments will also be accounted for. Costs will be standardized across years using the U.S. Consumer Price Index and presented in U.S. dollars.[12]

were not guided by economic hypotheses involving statistical tests and sample size calculations for incremental cost-effectiveness ratios were never attempted.

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